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Research paper

Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial

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ABSTRACT

Background: Several studies indicate that ketamine has rapid antidepressant effects in patients with treatment-resistant depression (TRD). The extent to which repeated doses of ketamine (versus placebo) reduce depression in the short and long term among outpatients with TRD *and chronic, current suicidal ideation* remains unknown.
Methods: Twenty-six medicated outpatients with severe major depressive disorder with current, chronic suicidal ideation were randomized in a double-blind fashion to six ketamine infusions (0.5 mg/kg over 45 minutes) or saline placebo over three weeks. Depression and suicidal ideation were assessed at baseline, 240 min post-infusion, and during a three-month follow-up phase.
Results: During the infusion phase, there was no differences in depression severity or suicidal ideation between placebo and ketamine ($p = 0.47$ and $p = 0.32$, respectively). At the end of the infusion phase, two patients in the ketamine group and one in the placebo group met criteria for remission of depression. At three-month follow-up, two patients in each group met criteria for remission from depression.
Limitations: Limitations include the small sample size, uncontrolled outpatient medication regimens, and restriction to outpatients, which may have resulted in lower levels of suicidal ideation than would be seen in emergency or inpatient settings.
Conclusions: Repeated, non-escalating doses of ketamine did not outperform placebo in this double-blind, placebo controlled study of patients with severe TRD and current, chronic suicidal ideation. This result may support our previously published open-label data that, in this severely and chronically ill outpatient population, the commonly used dose of 0.5 mg/kg is not sufficient.

1. Introduction

Major depressive disorder (MDD) is a very common psychiatric disorder, impacting between 7.0 and 12% of men and between 20.0 and 25.0% of women in the general population (Kessler et al., 2003). Though numerous well-established treatments for MDD exist (e.g., antidepressants, psychotherapy, somatic interventions), approximately 30% of MDD patients remain symptomatic, even after multiple adequate medication trials (Rush et al., 2009). Risk of hospitalization among such patients with "treatment-resistant depression" (TRD) is at

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least twice as high, and TRD patients incur significantly higher costs than their non-treatment-resistant, depressed (Crown et al., 2002). Chronic suicidal ideation (SI) is also common among individuals with TRD, who are more likely to engage in suicidal behavior than treatment responders (Souery et al., 2007). Patients with TRD *and* SI are an especially difficult-to-treat group, as patients with SI also tend to respond less well to antidepressants in the short term (Lopez-Castroman et al., 2016). Unfortunately, given the severity of their illness, high number of failed treatment trials, and elevated suicide risk, individuals with TRD and current, significant SI are often excluded from clinical trials, which has impeded the much-needed development of novel interventions for this high-risk population.

In recent years, increasing attention has been paid to an agent that may provide a gateway to the discovery of new antidepressant (and possibly anti-suicidal) treatments, ketamine. As opposed to currently-approved FDA approved antidepressants—which primarily are thought to modulate monoaminergic neurotransmitters—ketamine's glutamatergic modulation properties may be important for its effects on depression. Originally approved by the FDA as an anesthetic in 1970, ketamine is at the center of much psychiatric research for its rapid, robust, and relatively sustained (up to a week or more) antidepressant properties (Bobo et al., 2016; Coyle and Laws, 2015; McGirr et al., 2015; Newport et al., 2015; Romeo et al., 2015; Singh et al., 2017). Among TRD patients specifically, multiple randomized and open-label trials have shown ketamine infusions to produce acute reductions in depressive symptoms compared to placebo conditions.(Cusin et al., 2017; Diamond et al., 2014; Mathew et al., 2010; Murrough et al., 2013; Singh et al., 2016; Zarate et al., 2006) One recent double-blind, randomized, placebo-controlled trial also showed both twice-weekly and thrice-weekly dosing regimens of ketamine (0.5 mg/kg) to maintain antidepressant efficacy across a 15-day assessment periods among TRD outpatients (Singh et al., 2016). Additionally, findings indicate that ketamine may also have rapid antisuicidal properties with minimal side effects (Ballard et al., 2014; Canuso et al., 2018; DiazGranados et al., 2010; Grunebaum et al., 2018; Ionescu et al., 2016; Price et al., 2014, 2009; Reinstatler and Youssef, 2015; Wilkinson and Sanacora, 2016).

However, with recent notable exceptions (Canuso et al., 2018; Grunebaum et al., 2018) most previous studies of ketamine for TRD (and SI in the context of depression) are limited by the fact that patients with high suicide risk have often been excluded from participation (Cusin et al., 2017; Murrough et al., 2013; Singh et al., 2016). In addition, results from studies designed to assess the extent to which ketamine's antidepressant effects are sustained over longer periods of time (e.g., two weeks post-administration), are mixed (Coyle and Laws, 2015; Newport et al., 2015; Romeo et al., 2015). Finally, studies specifically examining the *antisuicidal* properties of ketamine among TRD populations have largely used very short follow-up periods or open-label or case study designs (Ballard et al., 2014; DiazGranados et al., 2010; Price et al., 2014, 2009) with several notable (and very recent) exceptions of randomized, double-blind, placebo-controlled studies of ketamine for patients at imminent risk of suicide (Canuso et al., 2018; Grunebaum et al., 2018, 2017). Though growing recent evidence in this area is promising, the extent to which repeated doses of ketamine (versus placebo) reduce depressive symptoms, including thoughts of suicide, in the short term and long term among TRD outpatients *with current and chronic SI* remains understudied and not well understood.

To explore this issue, our primary aim was to examine the short-term *and* long-term antidepressant efficacy of repeated-dose (0.5 mg/kg) ketamine augmentation compared to placebo in medicated, TRD outpatients with chronic SI. Given the outpatient setting in which this research was conducted, we excluded patients in need of immediate hospitalization for suicide risk; however, as our aim was to examine a population with the highest level of suicidality typically seen in outpatient settings, we *required* that participants report distressing levels of SI for at least 3 months. Our secondary aim was to examine ketamine's antisuicidal effects compared to placebo. We hypothesized that ketamine would have rapid and superior antidepressant and anti-suicidal efficacy compared to placebo. We also hypothesized that ketamine's antidepressant and antisuicidal efficacy would persist for a period of time after the final infusion in a small group of patients, based on the results of our previously published open-label study (Ionescu et al., 2016).

2. Methods

2.1. Patient selection

This study was approved at the Massachusetts General Hospital (MGH) by the Partners Human Research Committee (Institutional Review Board; IRB) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Prior to study entrance, all patients provided written, informed consent. This study is registered on the ClinicalTrials.gov Registry with (http://www.clinicaltrials.gov; NCT01582945). All procedures were conducted at the MGH.

Outpatients were recruited primarily through referrals. Inclusion criteria were: (1) 18–65 years old; (2) Primary diagnosis of current major depressive disorder (MDD), based on the Structured Clinical Interview for DSM-IV Diagnoses (SCID); (First et al., 1997) (3) Hamilton Depression Rating Scale, 28-Item (HDRS) (Hamilton, 1960) score ≥ 20 at screening; (4) History of ≥ 3 failed antidepressant treatment trials of adequate dose and duration during the current episode (including the current regimen), as measured by the MGH Antidepressant Treatment History Questionnaire (ATHQ); (Chandler et al., 2010) (5) SI for ≥ 3 months (as measured by ≥ 1 on the Columbia-Suicide Severity Rating Scale (C-SSRS) SI score (Posner et al., 2011) without the requirement for immediate hospitalization, *and* have a HDRS suicide item score ≥ 2 (current SI, thoughts of own death) at screening or one of the other two pre-infusion phase visits; (6) Ability to remain on an adequate, stable antidepressant regimen (on- and off-label treatments) for ≥ 4 weeks prior to infusions; (7) Ability to secure a reliable adult chaperone after ketamine infusion days; and (8) Maintain a treating psychiatrist in agreement with study participation, and who was aware of the safety plan in the protocol.

Exclusionary criteria were as follows: (1) pregnancy; (2) unstable medical illness; (3) bipolar disorder; (4) past multiple adverse drug reactions; (4) psychotic illness; (5) substance use disorder within the past year; (6) positive urine toxicology; (7) past history of ketamine abuse; (8) SI requiring immediate hospitalization or indicating immediate risk. In addition, although patients were maintained on their stable outpatient medication regimens prior to the start of the study and during infusions, certain medications were exclusionary due to risk of interactions: St. John's wort, theophylline, tramadol, and any use of illicit narcotics or barbiturates within the previous six months.

All patients were physically healthy as determined by physical exam, blood laboratory testing, electrocardiogram, and medical history obtained by a board-certified physician. Because participants were outpatients with current and clinically significant SI, ethical concerns prevented the tapering of current on-and-off label antidepressant regimens; the risks versus benefits of tapering patients off medications for research were deemed too great by the IRB. Therefore, patients were required to maintain their current antidepressant medication regimen stable for at least four weeks prior to the start of the study and for the duration of the ketamine infusions. Patients on a stable regimen of benzodiazepines for sleep or anxiety were instructed take their last dose no closer to infusion than the prior evening.

2.2. Study design and treatment

This double-blind, placebo controlled study was conducted between January 2013 and November 2015. During the “pre-infusion” phase patients were screened by a trained study clinician. After the initial screening visit, patients were evaluated in the clinic twice more within

two weeks, as we have observed in prior studies that a percentage of patients report a noticeable improvement in mood after being enrolled in a ketamine treatment study but prior to procedures being performed. The purpose of these first three visits was to (1) verify that patients continued to meet inclusion criteria for the study, (2) examine the stability of SI from screening through the pre-infusion phase, and (3) verify that patients remained on a stable medication regimen for at least four weeks prior to receiving the ketamine infusions. The third pre-infusion phase visit (i.e., the last visit before the active phase) was considered the "baseline."

If participants continued to meet entry criteria after this pre-infusion phase, they were admitted as outpatients to the Clinical Research Center (CRC) at MGH for the infusions ("infusion phase"). Infusions were generally scheduled to start at the same time of day (i.e., morning), and on the same two days each week, in an attempt to keep the administrations as consistent as possible. Patients were randomized (immediately following the pre-infusion phase) to receive six 45 min intravenous infusions of either ketamine (0.5 mg/kg) or saline placebo, over three weeks (two infusions per week). Group allocation was completed by a computer-generated randomization algorithm. The randomization list was maintained in a locked cabinet by a senior anesthesiologist. All clinicians, patients, and raters were blind to the randomization assignments. During the infusion, a board-certified anesthesiologist or psychiatrist programmed the infusion pump, and a physician remained present for the entire infusion. During the infusion, a nurse recorded vital signs (heart rate, blood pressure, respirations, pulse oximetry) and clinical status every 5 min. Any concerning or intolerable treatment-emergent side effects (e.g., hemodynamic instability, severe dissociation, worsening depression, or anxiety) prompted discontinuation of the infusion. Side effects were monitored 30 min prior to the infusion (for a baseline evaluation), every 5 min during the infusion, and for two hours post-infusion. At the end of each infusion, patients were clinically monitored for at least an additional two hours by the nursing staff in the CRC. Afterwards, a study doctor administered assessments of depression and SI (see *Outcome Measures*) at the four-hour post-infusion timepoint. At the completion of the visit, patients were discharged home with a responsible adult.

After the completion of the six infusions, follow-up visits occurred every other week for 3-months ("follow-up phase"). Visits were conducted in person or via telephone. During this naturalistic follow-up, necessary medication adjustments were allowed (per clinical judgment of the treating psychiatrist and were recorded by a study clinician). Throughout the entire study—pre-infusion, infusion, and follow-up phases—patients were evaluated a total of 15 times. The full trial protocol is available from the Principal Investigator by request.

2.3. Outcome measures

The primary outcome measure for assessing ketamine's antisuicidal efficacy compared to placebo was HDRS total score. The HDRS is a clinician-administered, 28-item rating scale that assesses symptoms of depression experienced over the past week. Response was defined as a ≥ 50% improvement on the HDRS; (Diamond et al., 2014; Hamilton, 1960) a HDRS score ≤ 7 was considered remission.

The secondary outcome was SI, measured with both the C-SSRS SI score and C-SSRS SI intensity rating (see the C-SSRS Scoring and Data Analysis Guide, Version 2.0 (February 2013)) (Posner et al., 2011). C-SSRS SI score captures the presence of suicidal thoughts, as rated on a 5-point ordinal scale. Absence of SI was defined as C-SSRS SI score = 0. C-SSRS SI intensity rating refers to the intensity of SI, as rated on a 5-point ordinal scale for five items: frequency, duration, controllability, deterrents, and reason for ideation. Total C-SSRS SI intensity ratings range from 0 to 25, with 25 indicating the most severe SI. The Clinician Administered Dissociative States Scale (CADSS)(Bremner et al., 1998) was also administered immediately prior to and after the start of the ketamine infusion at 30, 60, and 120 min to assess dissociative effects.

During the infusion phase, depression and SI rating scales were administered approximately 240 min (4 h) after the start of each infusion. At all visits, patients were asked to rate their overall symptoms based on the period since the last visit/infusion.

2.4. Statistical analysis

Demographic variables were compared using frequencies and chi-square analyses for categorical variables and *t*-tests for continuous variables.

For the analysis of depression (primary outcome; HDRS total score) and SI (secondary outcome; C-SSRS SI score and C-SSRS SI intensity rating), the intent-to-treat (ITT) model was utilized to include all patients. A mixed effect model with repeated measures (MMRM) approach was used to model the interaction effect of group x time for all efficacy analyses. Following the screening, an additional two evaluations were conducted to ensure that patients continued to meet eligibility criteria for the study throughout the pre-infusion phase; the third pre-infusion phase visit was used as the baseline for analysis, since this was the visit closest to the start of the infusions. Baseline scores were controlled for in all MMRM models. For visual purposes, all pre-infusion visit values are included in Fig. 1.

All tests were conducted with a significance level of $p < 0.05$ (2-sided), using STATA SE Version 12 statistical software (StataCorp LP, College Station, TX). Based on prior studies reporting moderate-to-large effect sizes in similar samples,(Bobo et al., 2016; Cusin et al., 2017) we also expected to observe large effect sizes.

3. Results

3.1. Demographics

There were no differences between the ketamine vs. placebo group with regard to age, sex, race, history of self-harm, history of trauma/abuse, family history of suicide, history of failed ECT, age of first depressive episode, number of past suicide attempts, number of failed medication trials in the current episode, length of current depressive episode, number of lifetime depressive episodes, or drug dose (based on weight); all *p*'s > 0.05. See Tables 1 and 2 for other specific demographic information.

3.2. Treatment participation

A total of 37 outpatients signed informed consent and were screened for study inclusion/exclusion criteria. Of these patients, 26 met all

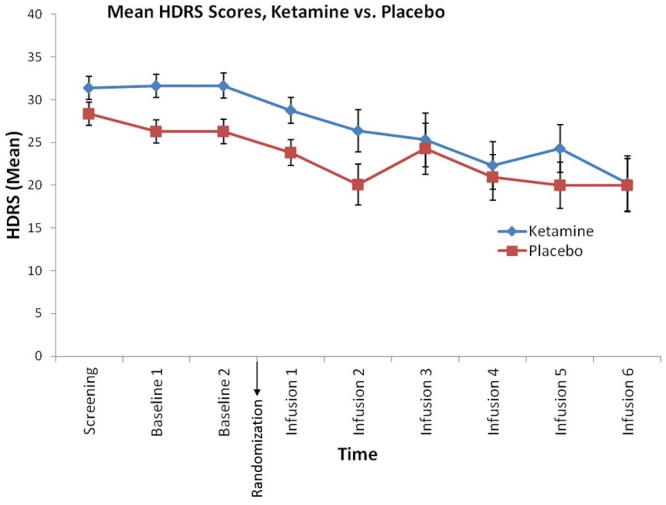

Fig. 1. Mean HDRS scores, ketamine vs. placebo.

Table 1.
Demographic and illness characteristics.

	Total Sample (n = 26)	Ketamine (n = 13)	Placebo (n = 13)	Range	p-value
Age	45.4 ± 12.4	45.5 ± 13.6	45.3 ± 11.7	21–65	0.52
Age of first depressive episode	19.3 ± 12.6	23.7 ± 15.4	14.6 ± 6.2	4–55	0.07
Number of past suicide attempts	1.6 ± 3.4	2.2 ± 4.6	1 ± 1.6	0–17	0.35
Number of failed medication trials	7.2 ± 3	6.6 ± 2.9	8.2 ± 3.1	3–13	0.63
Length of current episode of depression (Months)	115 ± 141.3 Median: 60	132.5 ± 154.6 Median: 66	91.6 ± 126.4 Median: 48	1.5–504	0.63
Number of lifetime depressive episodes	5.3 ± 6.7	5.2 ± 8.2	5.4 ± 5.2	1–25	0.26
Drug dose, based on weight (mg)	45.7 ± 11.7	44.9 ± 12.8	46.6 ± 10.8	26–70	0.52
	Total Sample (n = 26)	**Ketamine (n = 13)**	**Placebo (n = 13)**	***p*-value**	
Sex (Female)	10 (38%)	7 (54%)	3 (23%)	0.11	
Race (Caucasian)	21 (81%)	11 (85%)	10 (77%)	0.28	
History of self harm	8 (31%)	4 (31%)	4 (31%)	1.0	
History of trauma or abuse	10 (38%)	6 (46%)	4 (31%)	0.42	
Family history of suicide (n = 23)[a]	8 (35%)	5 (22%)	3 (13%)	0.30	
Failed ECT (n = 25)[a]	11 (44%)	6 (46%)	5 (38%)	0.83	

Abbreviation: ECT = Electroconvulsive Therapy.
[a] Percentages were calculated based on the number of patients with available data, not based on total sample size.

study criteria and were randomized to ketamine or placebo. Reasons for screen failures included time-commitment issues (n = 2 subjects), inadequate number of treatment failures (n = 2), preference to try approved treatments (n = 2), inadequate length of episode (n = 1), bipolar diagnosis (n = 1), concerns pertaining to cardiac risk (n = 1), positive toxicology screen for substance of abuse (n = 1), and becoming lost to follow up prior to infusions (n = 1).

During the infusion phase of the study, 9 of the 13 (69%) patients randomized to ketamine and 9 of the 13 patients randomized to placebo completed all six infusions. One patient randomized to placebo missed the fourth infusion due to inpatient hospitalization for SI, but otherwise completed the other visits.

One patient randomized to ketamine stopped the infusion due to hallucinatory side effects and was discontinued from the study; no post-infusion depression or SI data were collected for this participant. Two patients in the ketamine group withdrew before receiving their second infusion due to side effects, and one patient withdrew after three infusions because he did not believe the treatment was helping. In the

Table 2.
Concomitant medications.

Patient	Medication regimens	
	Antidepressant strategies (On and off-label)	Other concomitant agents
1	fluoxetine, bupropion	loratadine, corticosteroid PRN
3	selegiline, lamotrigine	
5	lithium	
6	venlafaxine, buspirone, lorazepam PRN	
8	phenelzine, lorazepam PRN	omeprazole, iron supplement, fish oil (omega-3 supplement)
10	tranylcypromine, trazodone, diazepam PRN, lorazepam	propranolol, diclofenac, ibuprofen, B-vitamin supplement, loratadine PRN, fexofenadine PRN, alprazolam
11	buspirone, hydroxyzine, dexedrine, ramelteon, guanfacine	
12	duloxetine, bupropion, clonazepam	levothyroxine, amlodipine, hyrochlorothiazide, losartan, omeprazole, fish oil (omega-3 supplement)
13	nortriptyline, lamotrigine, lurasidone	lisinopril, lubiprostone, Estratest, ondansetron PRN, omeprazole PRN, tramadol PRN
14	fluoxetine, hydroxyzine, amphetamine/dextroamphetamine, aripiprazole	levothyroxine, atenolol, progesterone and estrogen patch, atorvastatin
15	fluoxetine, venlafaxine, bupropion, alprazolam, lamotrigine, amphetamine/dextroamphetamine, lurasidone	
16	venlafaxine, bupropion, alprazolam, lurasidone	
17	vortioxetine, clonazepam, galantamine, methylphenidate, modafinil	gabapentin, omeprazole, simvastatin, zolpidem, acetaminophen PRN, pantoprazole, propanolol
18	clonazepam, lamotrigine, quetiapine, topiramate,	Famotidine, magnesium supplement, fish oil (omega-3 supplement), vitamin D supplement, probiotic supplement, sumatriptan PRN
19	amphetamine/dextroamphetamine	
20	venlafaxine, amphetamine/dextroamphetamine, alprazolam PRN	omeprazole, fexofenadine, finasteride, acetaminophen/hydrocodone, aspirin, fish oil (omega-3 supplement), potassium supplement, vitamin C supplement, SAM-e supplement, L-lysine supplement, gingko biloba supplement, acetaminophen/butalbital/caffeine PRN
23	duloxetine, lorazepam	oral contraceptive
24	fluvoxamine, lithium, lamotrigine, olanzapine, amphetamine/dextroamphetamine	levothyroxine
25	paroxetine, venlafaxine, clonazepam, quetiapine	lisinopril, allopurinol
26	paroxetine, lorazepam, depakote, amphetamine/dextroamphetamine	
27	lamotrigine, buproprion, amphetamine/dextroamphetamine	
29	venlafaxine	simvistatin, valsartan
30	bupropion, clonazepam, amphetamine/dextroamphetamine	ibuprofen PRN, triptan PRN
31	tranylcypromine, clonazepam, aripiprazole	
32	vortioxetine, bupropion, trazodone, clonazepam, buspirone, lisdexamfetamine, amphetamine/dextroamphetamine	propranolol, armodafinil, 4-Hydroxybutanoic acid
35	fluoxetine, lorazepam, prazosin	

Table 3.
Results of mixed model repeated measures analyses for depression and suicidal ideation rating scales.

		Screening[c]	Visit 1	Baseline[d]	Inf 1	Inf 2	Inf 3	Inf 4	Inf 5	Inf 6	Group effect*	Time effect*	Interaction*
Rating Scale		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	F, *p*	F, *p*	F, *p*
HDRS	*Ket*	31.4 ± 4.8	31.6 ± 4.5	31.6 ± 5.2	28.8 ± 5.2	26.4 ± 8.7	25.3 ± 10.7	22.3 ± 9.7	24.3 ± 9.7	20.2 ± 11.1	F(20) = 1.4, $p = 0.25$	F(19.5) = 5.5, $p < 0.01$	F(19.5) = 1, $p = 0.47$
Total	*Pbo*	28.4 ± 4.8	26.3 ± 4.5	26.3 ± 4.8	23.8 ± 5.2	20.1 ± 8.3	24.3 ± 10.4	20.9 ± 9.4	20 ± 9.4	20 ± 10.7			
C-SSRS	*Ket*	3 ± 1.4	2.2 ± 1.0	1.9 ± 1.0	1.9 ± 1.4	1.8 ± 1.0	1.6 ± 1.4	1.3 ± 1.4	1.1 ± 1.4	1.2 ± 1.4	F(23.7) = 0.35, $p = 0.85$	F(19.4) = 1.1, $p = 0.41$	F(19.4) = 1.3, $p = 0.32$
SI Score[b]	*Pbo*	3.2 ± 1.4	1.8 ± 1.0	1.4 ± 1.0	1.5 ± 1.4	1.1 ± 1.0	1.9 ± 1.4	1.5 ± 1.4	1.4 ± 1.4	1.4 ± 1.4			
C-SSRS	*Ket*	15.2 ± 4.2	14.8 ± 4.5	14.4 ± 5.2	13.1 ± 5.5	11.5 ± 6.9	8.9 ± 6.9	8.6 ± 7.6	7.7 ± 8.7	8.3 ± 9.0	F(22.9) = 0.49, $p = 0.49$	F(19.3) = 0.95, $p = 0.48$	F(19.6) = 1.5, $p = 0.23$
SI Intensity Rating	*Pbo*	16.6 ± 4.2	12.5 ± 4.5	12 ± 5.2	12 ± 5.5	11.2 ± 6.6	12.8 ± 6.9	11.7 ± 7.3	11.8 ± 8.3	11.1 ± 8.7			

Abbreviations: Inf = infusion; SD = standard deviation; Ket = ketamine; Pbo = placebo; HDRS = Hamilton depression rating Scale; C-SSRS = Columbia suicide severity rating scale.
[a] For inclusion, all patients must have had an HDRS-SI score ≥ 2 at screening, visit 1, or baseline.
[b] For inclusion, all patients must have had an C-SSRS SI score ≥ 1 at screening, visit 1, or baseline.
[c] Screening = Visit 0 (first visit to the clinic).
[d] Baseline = last visit prior to the start of the study drug infusions.
* Based on ratings from Baseline through Infusion 6.

placebo group, three patients withdrew after the first infusion due to belief of receiving placebo; no post-infusion depression or SI data were collected for one of these three participants. Overall, 24/26 randomized patients completed at least one set of post-infusion ratings.

3.3. Antidepressant efficacy: infusion phase

There was no significant change of HDRS total scores between the screening and baseline visit prior to randomization (Fig.1; $F(23.084) = 0.695$, $p = 0.51$), indicating that there was not a significant effect of simply being enrolled in the study on depression severity. There were no differences between ketamine vs. placebo groups on HDRS total score at any pre-infusion phase visit (Table 3; $p > 0.05$).

In the sample as a whole, depression decreased significantly across infusions (i.e., over time) (Table 3; $p < 0.01$). However, there were no statistically significant differences in HDRS total scores between the ketamine and placebo groups across infusions (i.e., group x time interaction) (Table 3; $p = 0.47$). Mean HDRS total scores for both the ketamine and placebo groups remained above 20 at the end of the infusions, suggesting that both groups remained at least moderately depressed.

After the final infusion, 3/12 (25%) subjects met criteria for antidepressant response in the ketamine group; 4/12 (33%) met criteria the placebo group. Two of 12 (17%) in the ketamine group and 1/12 (8%) in the placebo group met antidepressant remission criteria. There was no significant difference between the proportion of responders or remitters in the two groups (Table 4; all *p*'s > 0.05).

3.4. Antisuicidal efficacy: infusion phase

There was a significant effect of time on pre-infusion C-SSRS SI score, regardless of eventual randomization to ketamine or placebo ($F(23.806) = 14.679$, $p < 0.001$); specifically, the average C-SSRS SI score significantly decreased across the first three pre-infusion visits for the whole sample. There was not a significant effect of time on pre-infusion C-SSRS SI intensity ratings ($p > 0.05$). There were no group differences between ketamine vs. placebo on C-SSRS SI score or SI intensity rating at screening or baseline (Table 3; all *p*'s > 0.05). There was no significant group x time interaction between ketamine vs. placebo groups for the C-SSRS SI score (Table 3; $p = 0.32$) or C-SSRS SI intensity rating (Table 3; $p = 0.23$).

After the final infusion, 5/12 (42%) patients met criteria for absence of SI (i.e., C-SSRS SI score = 0) in the ketamine group, compared to 3/12 (25%) in the placebo group. Differences in absence of SI between groups were statistically insignificant (Table 5; $p > 0.05$).

3.5. CADSS differences: infusion phase

There was a significant difference between ketamine vs. placebo groups on mean CADSS total scores during the infusion visits, with patients in the ketamine group reporting higher dissociative symptoms (Fig. 2; $F(396) = 34.514$, $p < 0.001$). The largest difference between groups was at 30 min after the start of the infusion ($F(16.6) = 13.075$; $p < 0.01$).

3.6. Follow-up phase

In the three-month naturalistic follow up phase, 2 patients in the ketamine group and 2 in the placebo group were lost to follow-up. Overall, 14/26 total patients (54%) completed all visits (7 in the ketamine group and 7 in the placebo group).

Follow-up data were analyzed for depression efficacy at three months after the final infusion. At the end of follow-up, 2 (22%) of the remaining 9 patients in the ketamine group met criteria for both antidepressant response and antidepressant remission. In the placebo group, 3 (27%) of the remaining 11 patients met criteria for

Table 4.
Depression ratings after final infusion.

Rating scale		Remitters (*n*)	%	Statistics	Responders (*n*)	%	Statistics
HDRS Total score	*Ket*	2/12	17	$X^2 = 0.38$, df = 1, $p = 0.54$	3/12	25	$X^2 = 0.2$, df = 1, $p = 0.65$
	Pbo	1/12	8		4/12	33	

Table 5.
Suicidal ideation ratings after final infusion.

Rating Scale		Absence of SI (*n*)	%	Statistics
C-SSRS SI Score	*Ket*	5/12	42	$X^2 = 0.75$, df = 1, $p = 0.67$
	Pbo	3/12	25	

Abbreviations: Ket = ketamine; Pbo = placebo; HDRS = Hamilton depression rating scale; C-SSRS = Columbia suicide severity rating scale.

antidepressant response and 2/11 (18%) met criteria for antidepressant remission at the end of the three-month follow-up period. There was no significant difference between the proportion of responders or remitters in the two groups.

Of the 5 patients in the ketamine group who achieved absence of SI at the last infusion, 4 continued to meet absence of SI criteria at the beginning of the follow-up phase. Only 1 (11%) of the 9 remaining ketamine patients continued to have absence of SI at the end of the follow-up period. All 3 patients in the placebo group who had absence of SI at the last infusion continued to meet absence of SI criteria at the beginning of the follow-up phase, but only 2 of the remaining 10 placebo patients (20%) met absence of SI criteria at the end of the follow-up phase.

4. Discussion

In numerous published studies to date, ketamine has been shown to outperform control conditions in antidepressant efficacy among TRD individuals (Bobo et al., 2016). Results from recent studies also suggest the promising antisuicidal effects of ketamine (Ballard et al., 2014; Canuso et al., 2018; DiazGranados et al., 2010; Grunebaum et al., 2018; Ionescu et al., 2016; Price et al., 2014, 2009; Reinstatler and Youssef, 2015; Wilkinson and Sanacora, 2016). In contrast to earlier trials, in this double-blind, placebo controlled study of patients with severe TRD and current, chronic SI, ketamine *did not outperform placebo* in terms of short- or long-term antidepressant or antisuicidal efficacy. Specifically, there was no significant advantage of ketamine over placebo for improvements in depression, as measured by HDRS total scores. Ketamine treatment also did not have a significant advantage in terms of reducing SI, as measured with the C-SSRS.

There are several possible reasons why we did not observe a significant advantage of ketamine over placebo. First, the level of chronicity and treatment-resistance in this sample was higher than in most prior studies. Specifically, most patients had failed more than 5 adequate antidepressant trials in the current episode. Furthermore, nearly 50% of participants had prior failure to respond to ECT, and the average length of current major depressive episode was 115 months (9.6 years). Thus, it is possible that, among severely treatment-resistant patients, the traditional dose of ketamine (0.5 mg/kg over 40 min) used in this study was not sufficient to produce an improvement.

Of note, results from our previous open-label trial of *escalating repeated doses* of ketamine (0.5 mg/kg for the first three infusions to 0.75 mg/kg for the last three infusions) supported ketamine's antidepressant and antisuicidal properties in a sample of patients with similar baseline levels of depression and SI (Cusin et al., 2017; Ionescu et al., 2016). Importantly, in that open-label study, we began to see statistically significant antidepressant effects with a large effect size only when we increased the dose to 0.75 mg/kg ($p < 0.01$; Cohen's $d = 1.01$) (Cusin et al., 2017). Thus, for outpatients with treatment-resistant depression and chronic SI on concomitant medications, the increase of doses beyond the traditional 0.5 mg/kg over 40 min may be critical to achieve clinically significant effects. Toward this end, a single-infusion dose finding study was recently completed (Fava et al., in press) to examine the antidepressant efficacy of ketamine at doses of 0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg, and 1.0 mg/kg versus to the active comparator midazolam. Another possibility why we did not observe an advantage to ketamine is that the small sample rendered us vulnerable to Type II error (i.e., incorrect rejection of the null hypothesis). Last, though not statistically significant, the difference in percentage of females in the two conditions (54% versus 23% for ketamine versus placebo, respectively) may have impacted our results; however, there is not currently strong evidence to support sex differences in ketamine response (Niciu et al., 2014; Saland et al., 2017).

This study had a number of limitations. First, our sample was small primarily due to challenges with recruitment and retention. Of our 26 randomized patients, only 14 completed the entire study; this was due to multiple reasons, including the challenge for severely depressed patients to participate in such a time-intensive research study and lack of study resources to provide compensation. This may have left us underpowered to detect a true difference between the treatment groups.

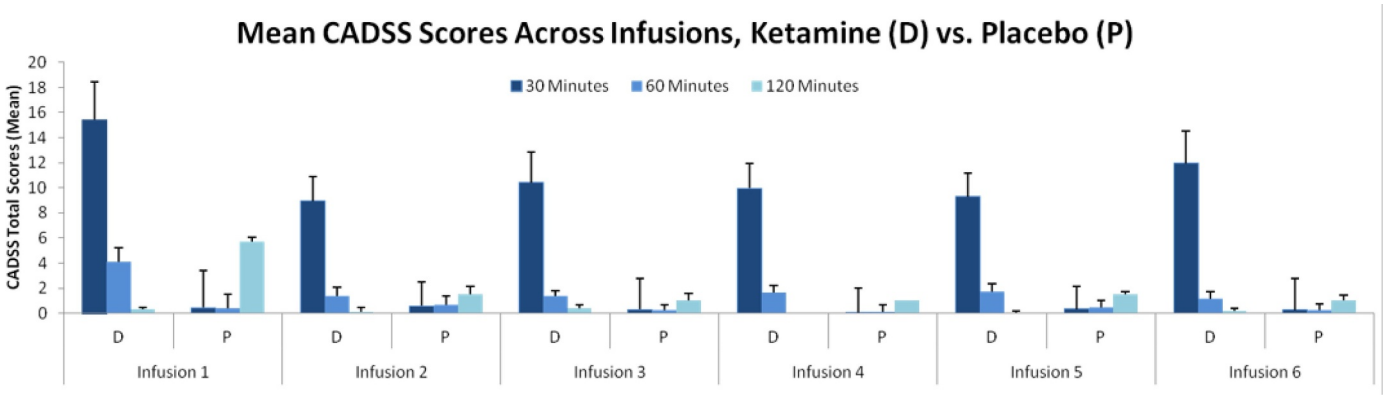

Fig. 2. Mean CADSS scores across infusions ketamine (D) vs. placebo (P).

Second, all patients were maintained on their outpatient medication regimens throughout the infusion phase. Therefore, we cannot rule out the impact that concomitant medications may have on ketamine's effects. Third, we examined *outpatients* with clinically significant and chronic SI; by definition, the suicide risk of these individuals was not imminent enough to warrant immediate hospitalization. Thus, we missed a large group of patients with more acute SI (e.g., in ER settings). Given that patients reporting chronic passive suicidal ideation still met our inclusion criteria, there may not have been significant room for change in SI. Because self-reported levels of SI were relatively low during the pre-infusion phase, we may have faced a "floor effect" that made it difficult to detect significant change in SI across the infusions. Fourth, all ratings were obtained at the 4-hour mark post-infusion; due to scheduling limitations, we did not assess same-day baselines. Perhaps other evaluation time points (e.g., 24 h, 48 h) would more acutely capture ketamine's effects. Last, we did not conduct symptom assessments during the week immediately following the final ketamine infusion, which did not allow us to assess the persistence of response over this one-week time frame.

Despite these limitations, this study also had notable strengths. First, our selection of TRD patients specifically for *current and chronic suicidal ideation* is a strength. Second, the use of a double-blind, placebo controlled trial is an important design advantage over our previous open-label study in a similar population (Cusin et al., 2017; Ionescu et al., 2016). Third, whereas many previous studies of ketamine examined only the short-term efficacy of this drug, we used a three-month follow-up period. Fourth, the purposeful inclusion of a lag time between enrollment and beginning the infusions allowed us to observe a significant decrease in C-SSRS SI scores during the pre-infusion phase. This suggests that even when recruitment is targeted at TRD patients with current, chronic SI, the effects of joining a time-intensive research study utilizing a drug like ketamine may yield treatment-independent improvements. In contrast, there was no significant pre-infusion decrease in depression scores. Patients with TRD are generally considered *less* likely to experience placebo response to treatment; (Sonawalla and Rosenbaum, 2002) however, these results suggest that separate processes may be involved in the improvement of SI vs. depressive symptoms.

Though the results of this small study were not significant, the investigation into ketamine's potential as a rapid antidepressant and antisuicidal agent merits continuation. In addition to studying ketamine in heterogeneous patient populations, future trials should focus on elucidating the specific subtypes of patients for whom ketamine is most effective in reducing chronic depression and perhaps, decreases suicidal thinking. For example, there are preliminary results to indicate that ketamine may have superior antidepressant properties among treatment-resistant patients with anxious depression as opposed to non-anxious depression (Ionescu et al., 2014). Further, recent research suggests that ketamine's antisuicidal effects may be correlated with its ability to improve sleep between the hours of 12 a.m. and 5 a.m., perhaps elucidating a certain subtype of patients with SI and insomnia (Ballard et al., 2016). Certainly, further exploration of ketamine's antidepressant and antisuicidal properties, particularly among treatment-resistant individuals, have the potential to lead to improved, targeted treatments for TRD and SI.

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Contributors

Dr. Dawn Ionescu, Dr. Jonathan Alpert, Dr. Emery Brown, Dr. Lee Baer, Dr. Matthew Nock, Dr. Maurizio Fava, and Dr. Cristina Cusin designed the study and wrote the protocol. All authors with the exception of Dr. Nock and Dr. Kate Bentley implemented the study protocol and contributed to data collection. Dr. Baer, Dr. Ionescu, Dr. Cusin, and Dr. Bentley statistically analyzed and interpreted the data. Dr. Ionescu wrote the first draft of the manuscript.

All authors contributed to and approved the final manuscript.

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Supplementary materials

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References

Ballard, E.D., Ionescu, D.F., Vande Voort, J.L., Niciu, M.J., Richards, E.M., Luckenbaugh, D.A., Brutsché, N.E., Ameli, R., Furey, M.L., Zarate, C.A., 2014. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J. Psychiatr. Res. 58, 161–166. https://doi.org/10.1016/j.jpsychires.2014.07.027.

Ballard, E.D., Vande Voort, J.L., Bernert, R.A., Luckenbaugh, D.A., Richards, E.M., Niciu, M.J., Furey, M.L., Duncan, W.C., Zarate, C.A., 2016. Nocturnal wakefulness is associated with next-day suicidal ideation in major depressive disorder and bipolar disorder. J. Clin. Psychiatry 825–831. https://doi.org/10.4088/JCP.15m09943.

Bobo, W.V., Vande Voort, J.L., Croarkin, P.E., Leung, J.G., Tye, S.J., Frye, M.A., 2016. Ketamine for treatment-resistant unipolar and bipolar major depression: critical review and implications for clinical practice. Depress. Anxiety 33, 698–710. https://doi.org/10.1002/da.22505.

Bremner, J.D., Krystal, J.H., Putnam, F.W., Southwick, S.M., Marmar, C., Charney, D.S., Mazure, C.M., 1998. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J. Trauma. Stress 11, 125–136. https://doi.org/10.1023/A:1024465317902.

Canuso, C.M., Singh, J.B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., Pinter, C., Hough, D., Sanacora, G., Manji, H., Drevets, W.C., 2018. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am. J. Psychiatry 175, 620–630. https://doi.org/10.1176/appi.ajp.2018.17060720.

Chandler, G.M., Iosifescu, D.V., Pollack, M.H., Targum, S.D., Fava, M., 2010. RESEARCH: validation of the massachusetts general hospital Antidepressant Treatment History Questionnaire (ATRQ). CNS Neurosci. Ther. 16, 322–325. https://doi.org/10.1111/j.1755-5949.2009.00102.x.

Coyle, C.M., Laws, K.R., 2015. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum. Psychopharmacol. Clin. Exp. 30, 152–163. https://doi.org/10.1002/hup.2475.

Crown, W.H., Finkelstein, S., Berndt, E.R., Ling, D., Poret, A.W., Rush, A.J., Russell, J.M., 2002. The impact of treatment-resistant depression on health care utilization and costs. J. Clin. Psychiatry 63, 963–971.

Cusin, C., Ionescu, D.F., Pavone, K.J., Akeju, O., Cassano, P., Taylor, N., Eikermann, M., Durham, K., Swee, M.B., Chang, T., Dording, C., Soskin, D., Kelley, J., Mischoulon, D., Brown, E.N., Fava, M., 2017. Ketamine augmentation for outpatients with treatment-resistant depression: preliminary evidence for two-step intravenous dose escalation. Aust. N. Z. J. Psychiatry 51, 55–64. https://doi.org/10.1177/0004867416631828.

Diamond, P.R., Farmery, A.D., Atkinson, S., Haldar, J., Williams, N., Cowen, P.J., Geddes, J.R., McShane, R., 2014. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J. Psychopharmacol. 28, 536–544. https://doi.org/10.1177/0269881114527361.

DiazGranados, N., Ibrahim, L.A., Brutsche, N.E., Ameli, R., Henter, I.D., Luckenbaugh, D.A., Machado-Vieira, R., Zarate, C.A., 2010. Rapid resolution of suicidal ideation after a single infusion of an N-Methyl-D-Aspartate antagonist in patients with treatment-resistant major depressive disorder. J. Clin. Psychiatry 71, 1605–1611. https://doi.org/10.4088/JCP.09m05327blu.

Fava, M., Freeman, M.P., Flynn, M., Judge, H., Hoeppner, B.B., Cusin, C., Ionescu, D.F., Mathew, S.J., Chang, L.C., Iosifescu, D.V., Murrough, J., Debattista, C., Schatzberg, A. F., Trivedi, M.H., Jha, M.K., Sanacora, G., Wilkinson, S.T., Papakostas, G.I. (in press). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD), Mol. Psychiatry.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders. American Psychiatric Press, Washington, D.C.

Grunebaum, M.F., Ellis, S.P., Keilp, J.G., Moitra, V.K., Cooper, T.B., Marver, J.E., Burke, A.K., Milak, M.S., Sublette, M.E., Oquendo, M.A., Mann, J.J., 2017. Ketamine versus midazolam in bipolar depression with suicidal thoughts: a pilot midazolam-controlled randomized clinical trial. Bipolar Disord. 19, 176–183. https://doi.org/10.1111/bdi.12487.

Grunebaum, M.F., Galfalcy, H.C., Choo, T.H., Keilp, J.G., Moitra, V.K., Parris, M.S., Marver, J.E., Burke, A.K., Milak, M.S., Sublette, M.E., Oquendo, M.A., Mann, J.J., 2018. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am. J. Psychiatry 175, 327–335. https://doi.org/10.1176/appi.ajp.2017.17060647.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Ionescu, D.F., Luckenbaugh, D.A., Niciu, M.J., Richards, E.M., Slonena, E.E., Vande Voort, J.L., Brutsche, N.E., Zarate, C.A., 2014. Effect of baseline anxious depression on initial and sustained antidepressant response to Ketamine. J. Clin. Psychiatry 75, e932–e938. https://doi.org/10.4088/JCP.14m09049.

Ionescu, D.F., Swee, M.B., Pavone, K.J., Taylor, N., Akeju, O., Baer, L., Nyer, M., Cassano, P., Mischoulon, D., Alpert, J.E., Brown, E.N., Nock, M.K., Fava, M., Cusin, C., 2016. Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine. J. Clin. Psychiatry e719–e725. https://doi.org/10.4088/JCP.15m10056.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of major depressive disorder. JAMA 289, 3095. https://doi.org/10.1001/jama.289.23.3095.

Lopez-Castroman, J., Jaussent, I., Gorwood, P., Courtet, P., 2016. Suicidal depressed patients respond less well to antidepressants in the short term. Depress. Anxiety 33, 483–494. https://doi.org/10.1002/da.22473.

Mathew, S.J., Murrough, J.W., aan het Rot, M., Collins, K.A., Reich, D.L., Charney, D.S., 2010. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. Int. J. Neuropsychopharmacol. 13, 71–82. https://doi.org/10.1017/S1461145709000169.

McGirr, A., Berlim, M.T., Bond, D.J., Fleck, M.P., Yatham, L.N., Lam, R.W., 2015. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol. Med. 45, 693–704. https://doi.org/10.1017/S0033291714001603.

Murrough, J.W., Iosifescu, D.V., Chang, L.C., Al Jurdi, R.K., Green, C.E., Perez, A.M., Iqbal, S., Pillemer, S., Foulkes, A., Shah, A., Charney, D.S., Mathew, S.J., 2013. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am. J. Psychiatry 170, 1134–1142. https://doi.org/10.1176/appi.ajp.2013.13030392.

Newport, D.J., Carpenter, L.L., McDonald, W.M., Potash, J.B., Tohen, M., Nemeroff, C.B., 2015. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am. J. Psychiatry 172, 950–966. https://doi.org/10.1176/appi.ajp.2015.15040465.

Niciu, N.J., Luckenbaugh, D.A., Ionescu, D.F., Guevara, S., Machado-Vieira, R., Richards, E.M., Brutsche, N.E., Nolan, N.M., Zarate, C.A., 2014. Clinical predictors of ketamine response in treatment-resistant depression. J. Clin. Psychiatry 75, e417–e423. https://doi.org/10.4088/JCP.13m08698.

Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia–suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168, 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704.

Price, R.B., Iosifescu, D.V., Murrough, J.W., Chang, L.C., Al Jurdi, R.K., Iqbal, S.Z., Soleimani, L., Charney, D.S., Foulkes, A.L., Mathew, S.J., 2014. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress. Anxiety 31, 335–343. https://doi.org/10.1002/da.22253.

Price, R.B., Nock, M.K., Charney, D.S., Mathew, S.J., 2009. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol. Psychiatry 66, 522–526. https://doi.org/10.1016/j.biopsych.2009.04.029.

Reinstatler, L., Youssef, N.A., 2015. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. Drugs R&D 15, 37–43. https://doi.org/10.1007/s40268-015-0081-0.

Romeo, B., Choucha, W., Fossati, P., Rotge, J.-Y., 2015. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. Psychiatry Res. 230, 682–688. https://doi.org/10.1016/j.psychres.2015.10.032.

Rush, A.J., Warden, D., Wisniewski, S.R., Fava, M., Trivedi, M.H., Gaynes, B.N., Nierenberg, A.A., 2009. STAR*D: revising conventional wisdom. CNS Drugs 23, 627–647. https://doi.org/10.2165/00023210-200923080-00001.

Saland, S.K., Duclot, F., Kabbaj, M., 2017. Integrative analysis of sex differences in the rapid antidepressant effects of ketamine in preclinical models for individualized clinical outcomes. Curr. Opin. Behav. Sci. 14, 19–26. https://doi.org/10.1016/j.cobeha.2016.11.002.

Singh, I., Morgan, C., Curran, V., Nutt, D., Schlag, A., McShane, R., 2017. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. Lancet Psychiatry 4, 419–426. https://doi.org/10.1016/S2215-0366(17)30102-5.

Singh, J.B., Fedgchin, M., Daly, E.J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J.W., Sanacora, G., Shelton, R.C., Kurian, B., Winokur, A., Fava, M., Manji, H., Drevets, W.C., Van Nueten, L., 2016. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am. J. Psychiatry 173, 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037.

Sonawalla, S.B., Rosenbaum, J.F., 2002. Placebo response in depression. Dialogues Clin. Neurosci. 4, 105–113.

Souery, D., Oswald, P., Massat, I., Bailer, U., Demyttenaere, K., Kasper, S., Lecrubier, Y., Montgomery, S., Serretti, A., Zohar, J., Mendlewicz, J., Group for the Study of Resistant Depression, 2007. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. J. Clin. Psychiatry 68, 1062–1070.

Wilkinson, S.T., Sanacora, G., 2016. Ketamine: a potential rapid-acting antisuicidal agent? Depress. Anxiety 33, 711–717. https://doi.org/10.1002/da.22498.

Zarate, C.A., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatry 63, 856. https://doi.org/10.1001/archpsyc.63.8.856.